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(54) Title: (5-(2-HYDROXY-4-CHLOROBENZOYL) AMINOVALERIC ACID AND SALTS THEREOF AND COMPOSITIONS
CONTAINING THE SAME FOR DELIVERING ACTIVE AGENTS

(57) Abstract: (5-(2-hydroxy-4-chlorobenzoyl) aminovaleric acid, salts thereof, and compositions containing the same for the de-
livery of active agents are provided. Methods of administration, treatment of disease and preparation are provided as well.

5 (5-(2-Hydroxy-4-chlorobenzoyl)aminovaleric
 Acid and Salts Thereof and Compositions
 Containing the Same for Delivering Active
 Agents

10 This application claims the benefit of U.S.
Provisional Application Nos. 60/230,332 and
60/237,234 filed September 6, 2000 and October 2,
2000, respectively, both of which are herein
incorporated by reference.

15

FIELD OF THE INVENTION

 The present invention relates to (5-(2-hydroxy-
4-chlorobenzoyl) aminovaleric acid and salts and
20 polymeric derivatives thereof compounds for
delivering active agents, such as biologically or
chemically active agents, to a target. These
compounds are well suited for forming non-covalent
mixtures with active agents for oral, intracolonic,
25 pulmonary, and other routes of administration to
animals. Methods for the preparation and
administration of such compositions are also
disclosed.

30

BACKGROUND OF THE INVENTION

 Conventional means for delivering active agents
are often severely limited by biological, chemical,
and physical barriers. Typically, these barriers
35 are imposed by the environment through which
delivery occurs, the environment of the target for

delivery, and/or the target itself. Biologically and chemically active agents are particularly vulnerable to such barriers.

In the delivery to animals of biologically
5 active and chemically active pharmacological and therapeutic agents, barriers are imposed by the body. Examples of physical barriers are the skin, lipid bi-layers and various organ membranes that are relatively impermeable to certain active agents but
10 must be traversed before reaching a target, such as the circulatory system. Chemical barriers include, but are not limited to, pH variations in the gastrointestinal (GI) tract and degrading enzymes.

These barriers are of particular significance
15 in the design of oral delivery systems. Oral delivery of many biologically or chemically active agents would be the route of choice for administration to animals if not for biological, chemical, and physical barriers. Among the numerous
20 agents which are not typically amenable to oral administration are biologically or chemically active peptides, such as calcitonin and insulin; polysaccharides, and in particular mucopolysaccharides including, but not limited to,
25 heparin; heparinoids; antibiotics; and other organic substances. These agents may be rapidly rendered ineffective or destroyed in the gastro-intestinal tract by acid hydrolysis, enzymes, and the like. In addition, the size and structure of macromolecular
30 drugs may prohibit absorption.

Earlier methods for orally administering vulnerable pharmacological agents have relied on the

co-administration of adjuvants (e.g., resorcinols and non-ionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to increase artificially the permeability of the intestinal walls, as well as the co-administration of enzymatic inhibitors (e.g., pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) and trasylol) to inhibit enzymatic degradation. Liposomes have also been described as drug delivery systems for insulin and heparin. However, broad spectrum use of such drug delivery systems is precluded because: (1) the systems require toxic amounts of adjuvants or inhibitors; (2) suitable low molecular weight cargos, i.e., active agents, are not available; (3) the systems exhibit poor stability and inadequate shelf life; (4) the systems are difficult to manufacture; (5) the systems fail to protect the active agent (cargo); (6) the systems adversely alter the active agent; or (7) the systems fail to allow or promote absorption of the active agent.

Proteinoid microspheres have been used to deliver pharmaceuticals. See, for example, U.S. Patent Nos. 5,401,516; 5,443,841; and Re. 35,862. In addition, certain modified amino acids have been used to deliver pharmaceuticals. See, for example, U.S. Patent Nos. 5,629,020; 5,643,957; 5,766,633; 5,776,888; and 5,866,536.

More recently, a polymer has been conjugated to a modified amino acid or a derivative thereof via a linkage group to provide for polymeric delivery agents. The modified polymer may be any polymer,

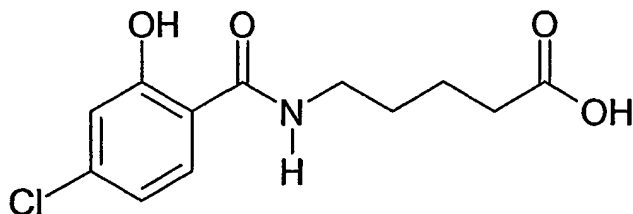
but preferred polymers include, but are not limited to, polyethylene glycol (PEG), and derivatives thereof. See, for example, International Patent Publication No. WO 00/40203.

5 However, there is still a need for simple, inexpensive delivery systems which are easily prepared and which can deliver a broad range of active agents by various routes.

10

SUMMARY OF THE INVENTION

The present invention provides compounds and compositions which facilitate the delivery of active agents. Delivery agent compounds of the present
15 invention include those having the following formula:



20

Compound 1

and salts thereof.

25 The invention also provides a composition comprising at least one of the delivery agent compound of the above formula, and at least one active agent. These compositions deliver active

agents to selected biological systems in increased or improved bioavailability of the active agent compared to administration of the active agent without the delivery agent compound.

5 Also provided are dosage unit forms comprising the compositions. The dosage unit may be in the form of a liquid or a solid, such as a tablet, capsule or particle, including a powder or sachet.

Another embodiment is a method for
10 administering an active agent to an animal in need of the active agent, by administering a composition comprising at one of the delivery agent compounds of the formula above and the active agent to the animal. Preferred routes of administration include
15 the oral, intracolonic and pulmonary routes.

Yet another embodiment is a method of treating a disease or for achieving a desired physiological effect in an animal in need thereof by administering an effective amount of the composition of the
20 present invention.

Yet another embodiment is a method of preparing a composition of the present invention by mixing at least one delivery agent compound of the formula above, and at least one active agent.

25

DETAILED DESCRIPTION OF THE INVENTION

Delivery Agent Compounds

30 The terms "alkyl" and "alkenyl" as used herein include linear and branched alkyl and alkenyl substituents, respectively.

The delivery agent compounds may be in the form of the carboxylic acid or salts thereof. Suitable salts include, but are not limited to, organic and inorganic salts, for example alkali-metal salts, such as sodium, potassium and lithium; alkaline-earth metal salts, such as magnesium, calcium or barium; ammonium salts; basic amino acids, such as lysine or arginine; and organic amines, such as dimethylamine or pyridine. Preferably, the salts are sodium salts. The salts may be mono- or multi-valent salts, such as monosodium salts and di-sodium salts. The salts may also be solvates, including ethanol solvates, and hydrates.

Salts of the delivery agent compounds of the present invention may be prepared by methods known in the art. For example, sodium salts may be prepared by dissolving the delivery agent compound in ethanol and adding aqueous sodium hydroxide.

In addition, poly amino acids and peptides comprising one or more of these delivery agent compounds may be used.

An amino acid is any carboxylic acid having at least one free amine group and includes naturally occurring and synthetic amino acids. Poly amino acids are either peptides (which are two or more amino acids joined by a peptide bond) or are two or more amino acids linked by a bond formed by other groups which can be linked by, e.g., an ester or an anhydride linkage. Peptides can vary in length from dipeptides with two amino acids to polypeptides with several hundred amino acids. One or more of the amino acids or peptide units may be acylated or

sulfonated.

The compounds described herein may be derived from amino acids and can be readily prepared from amino acids by methods within the skill of those in the art based upon the present disclosure and the methods described in International Patent Publication Nos. WO96/30036 and WO97/36480 and U.S. Patent Nos. 5,643,957 and 5,650,386. For example, the compounds may be prepared by reacting the single amino acid with the appropriate acylating or amine-modifying agent, which reacts with a free amino moiety present in the amino acid to form amides. Protecting groups may be used to avoid unwanted side reactions as would be known to those skilled in the art. With regard to protecting groups, reference is made to T.W. Greene, Protecting Groups in Organic Synthesis, Wiley, New York (1981), the disclosure of which is hereby incorporated herein by reference.

The delivery agent compound may be purified by recrystallization or by fractionation on one or more solid chromatographic supports, alone or linked in tandem. Suitable recrystallization solvent systems include, but are not limited to, ethanol, water, heptane, ethyl acetate, acetonitrile, methanol, tetrahydrofuran and mixtures thereof. Fractionation may be performed on a suitable chromatographic support such as alumina, using methanol/n-propanol mixtures as the mobile phase; reverse phase chromatography using trifluoroacetic acid/acetonitrile mixtures as the mobile phase; and ion exchange chromatography using water or an appropriate buffer as the mobile phase. When anion

exchange chromatography is performed, preferably a 0-500 mM sodium chloride gradient is employed.

The delivery agent compound may contain a polymer conjugated to it by a linkage group selected from the group consisting of -NHC(O)NH-, -C(O)NH-, -NHC(O), -OOC-, -COO-, -NHC(O)O-, -OC(O)NH-, -CH₂NH - NHCH₂-, -CH₂NHC(O)O-, -OC(O)NHCH₂-, -CH₂NHCOCH₂O-, -OCH₂C(O)NHCH₂-, -NHC(O)CH₂O-, -OCH₂C(O)NH-, -NH-, -O-, and carbon-carbon bond. According to one preferred embodiment, with the proviso that the polymeric delivery agent is not a polypeptide or polyamino acid. The polymer may be any polymer including, but not limited to, alternating copolymers, block copolymers and random copolymers, which are safe for use in mammals. Preferred polymers include, but are not limited to, polyethylene; polyacrylates; polymethacrylates; poly(oxyethylene); poly(propylene); polypropylene glycol; polyethylene glycol (PEG); and derivatives thereof and combinations thereof. The molecular weight of the polymer typically ranges from about 100 to about 200,000 daltons. The molecular weight of the polymer preferably ranges from about 200 to about 10,000 daltons. In one embodiment, the molecular weight of the polymer ranges from about 200 to about 600 daltons and more preferably ranges from about 300 to about 550 daltons.

Active Agents

Active agents suitable for use in the present invention include biologically active agents and chemically active agents, including, but not limited

to, pesticides, pharmacological agents, and therapeutic agents. Suitable active agents include those that are rendered less effective, ineffective or are destroyed in the gastro-intestinal tract by acid hydrolysis, enzymes and the like. Also included as suitable active agents are those macromolecular agents whose physiochemical characteristics, such as, size, structure or charge, prohibit or impede absorption when dosed orally.

For example, biologically or chemically active agents suitable for use in the present invention include, but are not limited to, proteins; polypeptides; peptides; hormones; polysaccharides, and particularly mixtures of muco-polysaccharides; carbohydrates; lipids; small polar organic molecules (i.e. polar organic molecules having a molecular weight of 500 daltons or less); other organic compounds; and particularly compounds which by themselves do not pass (or which pass only a fraction of the administered dose) through the gastro-intestinal mucosa and/or are susceptible to chemical cleavage by acids and enzymes in the gastro-intestinal tract; or any combination thereof. Further examples include, but are not limited to, the following, including synthetic, natural or recombinant sources thereof: growth hormones, including human growth hormones (hGH), recombinant human growth hormones (rhGH), bovine growth hormones, and porcine growth hormones; growth hormone releasing hormones; growth hormone releasing factor, interferons, including α , β and γ ;

interleukin-1; interleukin-2; insulin, including porcine, bovine, human, and human recombinant, optionally having counter ions including zinc, sodium, calcium and ammonium; insulin-like growth

5 factor, including IGF-1; heparin, including unfractionated heparin, heparinoids, dermatans, chondroitins, low molecular weight heparin, very low molecular weight heparin and ultra low molecular weight heparin; calcitonin, including salmon, eel,

10 porcine and human; erythropoietin; atrial natriuretic factor; antigens; monoclonal antibodies; somatostatin; protease inhibitors; adrenocorticotropin, gonadotropin releasing hormone; oxytocin; leutinizing-hormone-releasing-hormone;

15 follicle stimulating hormone; glucocerebrosidase; thrombopoietin; filgrastim; prostaglandins; cyclosporin; vasopressin; cromolyn sodium (sodium or disodium chromoglycate); vancomycin; desferrioxamine (DFO); bisphosphonates, including alendronate,

20 tiludronate, etidronate, clodronate, pamidronate, olpadronate, and incadronate; parathyroid hormone (PTH), including its fragments; antimicrobials, including antibiotics, anti-bacterials and anti-fungal agents; vitamins; analogs, fragments,

25 mimetics or polyethylene glycol (PEG)-modified derivatives of these compounds; or any combination thereof. Non-limiting examples of antibiotics include gram-positive acting, bacteriocidal, lipopeptidal and cyclic peptidal antibiotics, such

30 as daptomycin and analogs thereof.

Delivery systems

The composition of the present invention comprises one or more delivery agent compounds of the present invention (including their salts and
5 polymeric derivatives), and one or more active agents. In one embodiment, one or more of the delivery agent compounds, or salts of these compounds, or poly amino acids or peptides of which these compounds or salts form one or more of the
10 units thereof, may be used as a delivery may be used as a delivery agent by mixing with the active agent prior to administration to form an administration composition.

The administration compositions may be in the
15 form of a liquid. The solution medium may be water (for example, for salmon calcitonin, parathyroid hormone, and erythropoietin), 25% aqueous propylene glycol (for example, for heparin) and phosphate buffer (for example, for rhGH). Other dosing
20 vehicles include polyethylene glycol. Dosing solutions may be prepared by mixing a solution of the delivery agent compound with a solution of the active agent, just prior to administration. Alternately, a solution of the delivery agent
25 compound (or active agent) may be mixed with the solid form of the active agent (or delivery agent compound). The delivery agent compound and the active agent may also be mixed as dry powders. The delivery agent compound and the active agent can
30 also be admixed during the manufacturing process.

The dosing solutions may optionally contain additives such as phosphate buffer salts, citric

acid, glycols, or other dispersing agents.

Stabilizing additives may be incorporated into the solution, preferably at a concentration ranging between about 0.1 and 20% (w/v).

5 The administration compositions may alternately be in the form of a solid, such as a tablet, capsule or particle, such as a powder or sachet. Solid dosage forms may be prepared by mixing the solid form of the delivery agent compound with the solid
10 form of the active agent. Alternately, a solid may be obtained from a solution of the delivery agent compound and active agent by methods known in the art, such as freeze-drying (lyophilization), precipitation, crystallization and solid dispersion.

15

 The administration compositions of the present invention may also include one or more enzyme inhibitors. Such enzyme inhibitors include, but are not limited to, compounds such as actinonin or
20 epiactinonin and derivatives thereof. Other enzyme inhibitors include, but are not limited to, aprotinin (Trasylol) and Bowman-Birk inhibitor.

 The amount of active agent used in an administration composition of the present invention
25 is an amount effective to accomplish the purpose of the particular active agent for the target indication. The amount of active agent in the compositions typically is a pharmacologically, biologically, therapeutically, or chemically
30 effective amount. However, the amount can be less than that amount when the composition is used in a dosage unit form because the dosage unit form may

contain a plurality of delivery agent compound/active agent compositions or may contain a divided pharmacologically, biologically, therapeutically, or chemically effective amount. The
5 total effective amount can then be administered in cumulative units containing, in total, an effective amount of the active agent.

The total amount of active agent to be used can be determined by methods known to those skilled in
10 the art. However, because the compositions of the invention may deliver active agents more efficiently than compositions containing the active agent alone, lower amounts of biologically or chemically active agents than those used in prior dosage unit forms or
15 delivery systems can be administered to the subject, while still achieving the same blood levels and/or therapeutic effects.

The presently disclosed delivery agent compounds facilitate the delivery of biologically
20 and chemically active agents, particularly in oral, intranasal, sublingual, intraduodenal, subcutaneous, buccal, intracolonic, rectal, vaginal, mucosal, pulmonary, transdermal, intradermal, parenteral, intravenous, intramuscular and ocular systems, as
25 well as traversing the blood-brain barrier. Dosage unit forms can also include any one or combination of excipients, diluents, disintegrants, lubricants, plasticizers, colorants, flavorants, taste-masking agents, sugars, sweeteners, salts, and dosing
30 vehicles, including, but not limited to, water, 1,2-propane diol, ethanol, olive oil, or any combination thereof.

The compounds and compositions of the subject invention are useful for administering biologically or chemically active agents to any animals, including but not limited to, birds such as
5 chickens; mammals, such as rodents, cows, pigs, dogs, cats, primates, and particularly humans; and insects.

The system is particularly advantageous for delivering chemically or biologically active agents
10 that would otherwise be destroyed or rendered less effective by conditions encountered before the active agent reaches its target zone (i.e. the area in which the active agent of the delivery composition is to be released) and within the body
15 of the animal to which they are administered. Particularly, the delivery agent compounds and compositions of the present invention are useful in orally administering active agents, especially those that are not ordinarily orally deliverable, or those
20 for which improved delivery is desired.

The compositions comprising the delivery agent compounds and active agents have utility in the delivery of active agents to selected biological systems and in an increased or improved
25 bioavailability of the active agent compared to administration of the active agent without the delivery agent. Delivery can be improved by delivering more active agent over a period of time, or in delivering active agent in a particular time
30 period (such as to effect quicker or delayed delivery), or in delivering the active agent at a specific time, or over a period of time (such as

sustained delivery).

Another embodiment of the present invention is a method for the treatment or prevention of a disease or for achieving a desired physiological effect, such as those listed in the table below, in an animal by administering the composition of the present invention. Specific indications for active agents can be found in the Physicians' Desk Reference (54th Ed., 2000, Medical Economics Company, Inc., Montvale, NJ), which is herein incorporated by reference. The active agents in the table below include their analogs, fragments, mimetics, and polyethylene glycol-modified derivatives.

Active Agent	Disease and Physiological Effect
Growth hormones	Growth disorders
Interferons, including α , β and γ .	Viral infection, including chronic cancer and multiple sclerosis
Interleukin-1; interleukin-2.	Viral infection; cancer
Insulin; Insulin-like growth factor IGF-1.	Diabetes
Heparin	Thrombosis; prevention of blood coagulation
Calcitonin.	Osteoporosis; diseases of the bone
Erythropoietin	Anemia
Atrial natriuretic factor	Vasodilation
Antigens	Infection
Monoclonal antibodies	To prevent graft rejection; cancer
Somatostatin	Bleeding ulcer; erosive gastritis
Protease inhibitors	AIDS
Adrenocorticotropin	High cholesterol (to lower cholesterol)
Gonadotropin releasing hormone	Ovulatory dysfunction (to stimulate ovulation)
Oxytocin	Labor dysfunction (to stimulate contractions)

Active Agent	Disease and Physiological Effect
Leutinizing-hormone-releasing-hormone; follicle stimulating hormone	Regulate reproductive function
Glucocerebrosidase	Gaucher disease (to metabolize lipoprotein)
Thrombopoietin	Thrombocytopenia
Filgrastim	Reduce infection in chemotherapy patients
Prostaglandins	Hypertension
Cyclosporin	Transplant rejection
Vasopressin	Bed-wetting; antidiuretic
Cromolyn sodium; Vancomycin	Asthma; allergies
Desferrioxamine (DFO)	Iron overload
Parathyroid hormone (PTH), including its fragments.	Osteoporosis; Diseases of the bone
Antimicrobials	Infection including gram-positive bacterial infection
Vitamins	Vitamin deficiencies
Bisphosphonates	Osteoporosis; Paget's disease; Inhibits osteoclasts

For example, one embodiment of the present invention is a method for treating a patient suffering from or susceptible to diabetes by
5 administering insulin and at least one of the delivery agent compounds of the present invention.

Following administration, the active agent present in the composition or dosage unit form is taken up into the circulation. The bioavailability
10 of the agent is readily assessed by measuring a known pharmacological activity in blood, e.g. an increase in blood clotting time caused by heparin, or a decrease in circulating calcium levels caused by calcitonin. Alternately, the circulating levels
15 of the active agent itself can be measured directly.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate the invention without limitation. All parts are given by weight unless otherwise indicated.

5 Proton nuclear magnetic resonance (^1H NMR) analyses for the compounds listed below were conducted on a 300 MHz Bruker spectrometer using dimethyl sulfoxide ($\text{DMSO}-d_6$) as the solvent unless otherwise indicated.

10

Example 1 - Compound Preparation**Preparation of compound 1 (5-(2-hydroxy-4-chlorobenzoyl)aminovaleric acid).**

15 A 1-liter, 3-neck flask equipped with a Dean-Stark trap and condenser was charged with 170.47 g (0.988 mol) of 4-chlorosalicylic acid, 510 ml (413.1 g, 5.57 mol) of n-butanol and 4.0 ml (7.36 g, 0.075 mol) of sulfuric acid. The suspension was heated to
20 reflux. Over the course of 20 hours, 28 ml of water was removed via n-butanol azeotrope. The cooled reaction mixture was treated with 15 g of sodium bicarbonate, stirred for 30 minutes, washed with water (2 x 50 ml), dried over sodium sulfate and
25 concentrated. A total of 232 g of butyl ester (and n-butanol) was isolated.

 The ester and 800 ml of methanol were charged to a 2-liter, 3-neck flask equipped with an inlet attached to an ammonia cylinder and a reflux
30 condenser. Gaseous ammonia was added periodically over 20-40 minutes every 4 hours or so. Addition caused the temperature to rise as high as 45°C. The

progress of the reaction was monitored by HPLC. After 5 days and a total of 29 g (1.70 mol) of ammonia added, the reaction was complete. The reflux condenser was replaced by a distillation
5 apparatus, and distillation of methanol and residual ammonia was begun. A total of 300 ml of distillate was collected. Upon cooling to 25°C a solid formed. A total of 400 ml of water was added. The pH of the mixture was adjusted to 3.2 (from 9) with 4%
10 aqueous hydrochloric acid. The solid was isolated by filtration, rinsing with 500 ml of 1:1 methanol/water, 200 ml of 4% aqueous sodium bicarbonate solution and 400 ml of 4:1 hexanes/ethyl acetate. A total of 142.64 g of 4-
15 chlorosalicylamide was isolated.

A 1-liter flask equipped with an addition funnel was charged with 142.64 g (0.831 mol) of 4-chlorosalicylamide, 75 ml (73.35 g, 0.927 mol) of pyridine and 225 ml of acetonitrile. The slurry was
20 cooled in an ice bath, and 86.0 ml (97.61 g, 0.899 mol) of ethyl chloroformate was added dropwise over 50 minutes. The reaction mixture was stirred for 30 minutes and warmed to 25°C. The addition funnel was replaced by a distillation head. The
25 mixture was refluxed for 20 hours, distilling 200 ml of solvent off in the last 4 hours. The cooled slurry was diluted with 300 ml of 2% aqueous sodium bicarbonate solution. The resulting solid was filtered off to give 149.91 g of 7-chlorocarsalm,
30 after drying.

A 100 ml flask equipped with a reflux condenser

was charged with 4.47 g (22.6 mmol) of 7-chlorocarsalam, 3.55 ml (4.69 g, 22.4 mmol) of ethyl 5-bromovalerate, 35 ml of dimethylacetamide and 2.47 g (23.3 mmol) of sodium carbonate. The suspension
5 was heated to 70°C. After 3 hours, the reaction was complete. The cooled reaction mixture was filtered, rinsing with ethanol. The filtrate was diluted with 200 ml of water, causing a solid to develop. The solid was isolated by filtration. The wet cake was
10 taken up in 20 ml of ethanol and 40 ml of 2N aqueous sodium hydroxide solution. After refluxing for 3 hours, the mixture was cooled to 25°C and acidified with 4% aqueous hydrochloric acid. The resulting solid was isolated by filtration and recrystallized
15 to give 4.83 g of 5-(2-hydroxy-4-chlorobenzoyl)aminovaleric acid, mp 140-1°C.
Combustion analysis: %C: 53.05 (calc'd), 52.91 (found); %H: 5.19 (calc'd), 5.01 (found); %N: 5.16 (calc'd), 5.02 (found). ¹H NMR Analysis: (d6-DMSO): δ 13.0, s, 1H (COOH); δ 12.1, s, 1H (OH); δ 8.9, t, 1H, (NH); δ 7.9, d, 1H (aryl H ortho to amide); δ 7.0, m, 2H (other two aryl H); δ 3.3, q, 2H, (CH₂ α to N); δ 2.3, t, 2H (CH₂ α to COOH); δ 1.6, m, 4H (other two CH₂'s).

25

Example 2 - Cromolyn - Oral Delivery

Dosing solutions containing a delivery agent compound and cromolyn, disodium salt (cromolyn) (from Sigma Chemical of St. Louis, MO) were prepared in
30 deionized water. The free acid of the delivery agent compound was converted to the sodium salt with

one equivalent of sodium hydroxide. This mixture was vortexed and placed in a sonicator (about 37°C).

The pH was adjusted to about 7-7.5 with aqueous NaOH. Additional NaOH was added, if necessary, to
5 achieve uniform solubility, and the pH re-adjusted.

The mixture was vortexed to produce a uniform solution, also using sonication and heat if necessary. The delivery agent compound solution was mixed with cromolyn from a stock solution (175 mg
10 cromolyn/ml in deionized water, pH adjusted, if necessary, with NaOH or HCl to about 7.0, stock solution stored frozen wrapped in foil, then thawed and heated to about 30°C before using). The mixture was vortexed to produce a uniform solution, also
15 using sonication and heat if necessary. The pH was adjusted to about 7-7.5 with aqueous NaOH. The solution was then diluted with water to the desired volume (usually 2.0 ml) and concentration and stored wrapped in foil before use. The final delivery
20 agent compound and cromolyn doses, and the dose volumes are listed below in Table 1.

The typical dosing and sampling protocols were as follows. Male Sprague-Dawley rats weighing between 200-250g were fasted for 24 hours and were
25 anesthetized with ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing and again as needed to maintain anesthesia. A dosing group of five animals was administered one of the dosing solutions. An 11cm Rusch 8 French
30 catheter was adapted to a 1 ml syringe with a pipette tip. The syringe was filled with dosing

solution by drawing the solution through the catheter, which was then wiped dry. The catheter was placed down the esophagus leaving 1 cm of tubing past the incisors. Solution was administered by pressing the syringe plunger.

Blood samples were collected via the tail artery, typically at 0.25, 0.5, 1.0 and 1.5 hours after dosing. Serum cromolyn concentrations were measured by HPLC. Samples were prepared as follows:

- 10 100 μ l serum was combined with 100 μ l 3N HCl and 300 μ l ethyl acetate in an eppendorf tube. The tube was vortexed for 10 minutes and then centrifuged for 10 minutes at 10,000 rpm. 200 μ l ethyl acetate layer was transferred to an eppendorf tube
- 15 containing 67 μ l 0.1 M phosphate buffer. The tube was vortexed for 10 minutes and then centrifuged for 10 minutes at 10,000 rpm. The phosphate buffer layer was then transferred to an HPLC vial and injected into the HPLC (column = Keystone Exsil
- 20 Amino 150x2 mm i.d., 5 μ m, 100Å; mobile phase = 35% buffer(68 mM KH_2PO_4 adjusted to pH 3.0 with 85% H_3PO_4)/65% acetonitrile; injection volume = 10 μ l; flow rate = 0.30 ml/minute; cromolyn retention time = 5.5 minutes; absorbance detected at 240 nm).
- 25 Previous studies indicated baseline values of about zero.

Results from the animals in each group were averaged for each time point and the highest of these averages (i.e., mean peak serum cromolyn concentration) is reported below in Table 1.

Table 1. Cromolyn - Oral Delivery

Compound	Compound Dose (mg/kg)	Cromolyn Dose (mg/kg)	Volume dose (ml/kg)	Mean Peak serum [cromolyn] $\mu\text{g/ml}$ \pm SD
1	200	25	1	0.36 ± 0.42
1	200	25	1	0.08 ± 0

Example 3 - Interferon - Oral Delivery

5 Dosing solutions of the delivery agent compound and human interferon (IFN) were prepared in deionized water. The free acid of the delivery agent compound was converted to the sodium salt with one equivalent of sodium hydroxide. Typically, a
10 solution of the delivery agent compound was prepared in water and stirred, adding one equivalent of sodium hydroxide (1.0 N) when making the sodium salt. This mixture was vortexed and placed in a sonicator (about 37°C). The pH was adjusted to about
15 7.0 to 8.5 with aqueous NaOH. The mixture was vortexed to produce a uniform suspension or solution, also using sonication and heat if necessary. Additional NaOH was added, if necessary, to achieve uniform solubility, and the pH re-
20 adjusted. The delivery agent compound solution was mixed with an IFN stock solution (about 22.0 to 27.5 mg/ml in phosphate buffered saline) and diluting to the desired volume (usually 3.0 ml). The final delivery agent compound and IFN doses, and the dose
25 volumes are listed below in Table 2.

The typical dosing and sampling protocols were as follows. Male Sprague-Dawley rats weighing between 200-250g were fasted for 24 hours and

administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing and again as needed to maintain anesthesia. A dosing group of five animals was administered one of the dosing solutions. An 11cm Rusch 8 French catheter was adapted to a 1 ml syringe with a pipette tip. The syringe was filled with dosing solution by drawing the solution through the catheter, which was then wiped dry. The catheter was placed down the esophagus leaving 1 cm of tubing past the incisors. Solution was administered by pressing the syringe plunger.

Blood samples were collected serially from the tail artery, typically at time = 0, 15, 30, 45, 60 and 90 minutes. Serum IFN concentrations were quantified using Cytoscreen Immunoassay Kit for human IFN-alpha (catalog # KHC4012 from Biosource International, Camarillo, CA). Previous studies indicated baseline values of about zero. Results from the animals in each group were averaged for each time point. The maximum of these averages (i.e., the mean peak serum IFN concentration) is reported below in Table 2.

Table 2. Interferon - Oral Delivery

Compound	Compound Dose (mg/kg)	IFN Dose (mg/kg)	Volume dose (ml/kg)	Mean Peak Serum [IFN] (ng/ml) \pm SD
1	200	1.0	1.0	9.90 \pm 4.59

Example 4 - Insulin - Oral Delivery

Oral dosing (PO) compositions of delivery agent

compound and human zinc insulin (minimum 26 IU/mg available from Calbiochem - Novabiochem Corp, La Jolla, CA) were prepared in deionized water.

Typically, 500 mg of delivery agent compound was added to 1.5 ml of water. The free acid of the delivery agent compound was converted to the sodium salt by stirring the resultant solution and adding one equivalent of sodium hydroxide. The solution was vortexed, then heated (about 37°C) and sonicated.

The pH was adjusted to about 7 to 8.5 with NaOH or HCl. Additional NaOH was added, if necessary, to achieve uniform solubility, and the pH re-adjusted.

Water was then added to bring the total volume to about 2.4 ml and vortexed. About 1.25 mg insulin from an insulin stock solution (15 mg/ml made from 0.5409 g insulin and 18 ml deionized water, adjusting with HCl and NaOH to pH 8.15 and to obtain a clear solution using 40 ml concentrated HCl, 25 ml 10N NaOH and 50 ml 1N NaOH) was added to the solution and mixed by inverting. The final delivery agent compound dose, insulin dose and dose volume amounts are listed below in Table 3.

The typical dosing and sampling protocols were as follows. Male Sprague-Dawley rats weighing between about 200-250g were fasted for 24 hours and administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing and again as needed to maintain anesthesia. A dosing group of five animals was administered one of the dosing solutions. For oral dosing, an 11 cm Rusch 8 French catheter was adapted to a 1 ml syringe with a

pipette tip. The syringe was filled with dosing solution by drawing the solution through the catheter, which was then wiped dry. The catheter was placed down the esophagus leaving 1 cm of tubing
5 past the incisors. Solution was administered by pressing the syringe plunger.

Blood samples were collected serially from the tail artery, typically at time = 15, 30, 60, 120 and 180 minutes. Serum insulin levels were determined
10 with an Insulin ELISA Test Kit (Kit # DSL-10-1600 from Diagnostic Systems Laboratories, Inc., Webster, TX), modifying the standard protocol in order to optimize the sensitivity and linear range of the standard curve for the volumes and concentrations of
15 the samples used in the present protocol. Serum human insulin concentrations ($\mu\text{U}/\text{ml}$) were measured for each time point for each of the five animals in each dosing group. The five values for each time point were averaged and the results plotted as serum
20 insulin concentration versus time. (Previous experiments revealed no measurable levels of human insulin following oral dosing with human insulin alone.) Serum glucose levels were also measured. The maximum (peak) are reported below in Table 3.

25

Table 3. Insulin - Oral Delivery

Delivery Agent Compound #	Delivery Agent Compound Dose (mg/kg)	Insulin Dose (mg/kg)	Volume dose (ml/kg)	Mean Peak Serum Human Insulin ($\mu\text{U}/\text{ml} \pm \text{SD}$)	Mean Peak Serum Glucose Levels ($\mu\text{U}/\text{ml}$)
1	200	0.5	1.0	6.40 ± 3.18	36.25 ± 2.5

Example 5 - Daptomycin - Oral/Intracolonic
Delivery

Dosing solutions containing a delivery agent compound and daptomycin (Cubist Pharmaceuticals, Cambridge, MA) were prepared in 0.9% normal saline.

A solution of the compound was made either with the sodium salt of the compound or by converting the free acid to its sodium salt. The free acid of the delivery agent compound was converted to the sodium salt with one equivalent of sodium hydroxide. This mixture was vortexed and placed in a sonicator (about 37°C). The pH was adjusted to about 7.0-7.5 with aqueous HCl or NaOH. Additional NaOH was added, if necessary, to achieve uniform solubility, and the pH readjusted. The mixture was vortexed to produce a uniform solution, also using sonication if necessary. The delivery agent compound solution was mixed with daptomycin from a stock solution (200 mg daptomycin/mL in 0.9% normal saline and the pH adjusted, if necessary, to between 6.0-7.0 with NaOH or HCl). The stock solution was stored frozen (-20°C) wrapped in foil, then thawed and warmed gradually to about 25°C before using. The delivery agent-daptomycin mixture was vortexed at low speed to produce a uniform solution. The pH was adjusted to about 7.0-7.5 with aqueous NaOH. The solution was then diluted with 0.9% normal saline to the desired volume (usually 2.0 ml) and concentration and stored wrapped in foil before use. The final delivery agent compound and daptomycin doses, and the dose volumes are listed below in Table 4.

The typical dosing and sampling protocols were as follows. Male Sprague-Dawley rats weighing between 200-250 g were fasted for 24 hours and were anesthetized with ketamine (44 mg/kg) and thorazine (1.5 mg/kg) 15 minutes prior to dosing and again as needed to maintain anesthesia. A dosing group of five animals was administered one of the dosing solutions. For oral gavage (PO) dosing, an 11cm Rusch 8 French catheter was adapted to a 1 ml syringe with a pipette tip. The syringe was filled with dosing solution by drawing the solution through the catheter, which was then wiped dry. The catheter was placed down the esophagus leaving 1 cm of tubing past the incisors. Solution was administered by pressing the syringe plunger. For intracolonic (IC) dosing, a 7.5cm, 8 fr Rusch catheter was adapted to a 1 ml syringe with a pipette tip. The dosing catheter was inserted into the colon through the anus until the tube was no longer visible. The dosing solution was expressed slowly into the colon by pressing the syringe plunger.

Heparinized rat blood samples were collected via the ventral tail artery, typically at 0.25, 0.5, 0.75, 1.0, 2.0, and 4.0 hours after dosing, and stored on ice. Blood samples were then spun (centrifuged) at 11,500 rpm for 4 minutes at 4°C to obtain the plasma (supernatant), which was stored at -70°C. The plasma daptomycin concentrations were measured by isocratic reversed phase HPLC, keeping samples at 4°C during analysis. Blank plasma studies show baseline values of zero.

Results from the animals in each group were averaged for each time point and the highest of these averages (i.e., mean peak daptomycin concentration, C_{\max}) is reported below in Table 4.

5

Table 4. Daptomycin - Oral Delivery

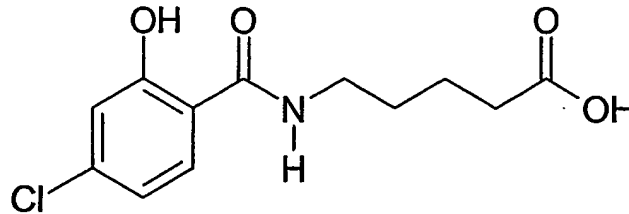
Delivery Agent Compound	Route of Administration	Delivery Agent Compound Dose (mg/kg)	Daptomycin Dose (mg/kg)	Volume dose (mL/kg)	Mean plasma C_{\max} [daptomycin] \pm SD, $\mu\text{g/mL}$
1	PO	200	50	1	9.82 \pm 6.80
1	IC	200	25	1	26.24 \pm 2.78
1	PO	200	50	1	12.74 \pm 8.37
1	PO	200	50	1	19.12 \pm 3.05
1	PO	200	50	2	13.38 \pm 3.53

The above-mentioned patents, applications, test
10 methods, and publications are hereby incorporated by reference in their entirety.

Many variations of the present invention will suggest themselves to those skilled in the art in light of the above detailed description. All such
15 obvious variations are within the fully intended scope of the appended claims.

WHAT IS CLAIMED IS:

- 1 1. A compound selected from the group consisting of



2 compound 1

3 and salts thereof.

- 1 2. A composition comprising:

- 2 (A) an active agent; and
3 (B) a compound selected from the group consisting
4 of compound 1, salts thereof, and mixtures
5 thereof.

1

- 1 3. The composition of **claim 2**, wherein the active agent is
2 selected from the group consisting of a biologically active
3 agent, a chemically active agent, and a combination thereof.

1

- 1 4. The composition of **claim 3**, wherein the biologically
2 active agent comprises at least one protein, polypeptide,
3 peptide, hormone, polysaccharide, mucopolysaccharide,
4 carbohydrate, or lipid.

- 1 5. The composition of **claim 3**, wherein the biologically
2 active agent is selected from the group consisting of:
3 growth hormones, human growth hormones (hGH), recombinant
4 human growth hormones (rhGH), bovine growth hormones, porcine

5 growth hormones, growth hormone-releasing hormones,
6 interferons, α -interferon, β -interferon, γ -interferon,
7 interleukin-1, interleukin-2, insulin, porcine insulin, bovine
8 insulin, human insulin, human recombinant insulin, insulin-
9 like growth factor(IGF), IGF-1, heparin, unfractionated
10 heparin, heparinoids, dermatans, chondroitins, low molecular
11 weight heparin, very low molecular weight heparin, ultra low
12 molecular weight heparin, calcitonin, salmon calcitonin, eel
13 calcitonin, human calcitonin; erythropoietin (EPO), atrial
14 natriuretic factor, antigens, monoclonal antibodies,
15 somatostatin, protease inhibitors, adrenocorticotropin,
16 gonadotropin releasing hormone, oxytocin, leutinizing-hormone-
17 releasing-hormone, follicle stimulating hormone,
18 glucocerebrosidase, thrombopoietin, filgrastim,
19 prostaglandins, cyclosporin, vasopressin, cromolyn sodium,
20 sodium chromoglycate, disodium chromoglycate, vancomycin,
21 desferrioxamine (DFO), parathyroid hormone (PTH), fragments of
22 PTH, antimicrobials, antibiotics, antibacterial agents, anti-
23 fungal agents, daptomycin, vitamins; analogs, fragments,
24 mimetics and polyethylene glycol (PEG)-modified derivatives of
25 these compounds; and any combination thereof.

1 6. The composition of **claim 3**, wherein the biologically
2 active agent comprises interferon, cromolyn sodium sodium
3 chromoglycate, disodium chromoglycate, daptomycin, analogs,
4 fragments, mimetics and polyethylene glycol (PEG)-modified
5 derivatives of these compounds or combinations thereof.

1 7. The composition of **claim 3**, wherein the biologically
2 active agent comprises interferon.

1 8. The composition of **claim 3**, wherein the biologically
2 active agent comprises sodium cromolyn.

1 9. The composition of **claim 3**, wherein the biologically

2 active agent comprises daptomycin, an analog thereof, or
3 mixtures thereof.

1 10. A dosage unit form comprising:
2 (A) the composition of **claim 2**; and
3 (B) (a) an excipient
4 (b) a diluent,
5 (c) a disintegrant,
6 (d) a lubricant,
7 (e) a plasticizer,
8 (f) a colorant,
9 (g) a dosing vehicle, or
10 (h) any combination thereof.

1 11. The dosage unit form of **claim 10**, wherein the active
2 agent is selected from the group consisting of a biologically
3 active agent, a chemically active agent, and a combination
4 thereof.

1 12. The dosage unit form of **claim 11**, wherein the
2 biologically active agent comprises at least one protein,
3 polypeptide, peptide, hormone, polysaccharide,
4 mucopolysaccharide, carbohydrate, or lipid.

1 13. The dosage unit form of **claim 11**, wherein the
2 biologically active agent is selected from the group
3 consisting of:
4 growth hormones, human growth hormones (hGH), recombinant
5 human growth hormones (rhGH), bovine growth hormones, porcine
6 growth hormones, growth hormone-releasing hormones,
7 interferons, α -interferon, β -interferon, γ -interferon,
8 interleukin-1, interleukin-2, insulin, porcine insulin, bovine
9 insulin, human insulin, human recombinant insulin, insulin-
10 like growth factor(IGF), IGF-1, heparin, unfractionated
11 heparin, heparinoids, dermatans, chondroitins, low molecular

12 weight heparin, very low molecular weight heparin, ultra low
13 molecular weight heparin, calcitonin, salmon calcitonin, eel
14 calcitonin, human calcitonin; erythropoietin (EPO), atrial
15 nuretic factor, antigens, monoclonal antibodies,
16 somatostatin, protease inhibitors, adrenocorticotropin,
17 gonadotropin releasing hormone, oxytocin, leutinizing-hormone-
18 releasing-hormone, follicle stimulating hormone,
19 glucocerebrosidase, thrombopoietin, filgrastim,
20 prostaglandins, cyclosporin, vasopressin, cromolyn sodium,
21 sodium chromoglycate, disodium chromoglycate, vancomycin,
22 desferrioxamine (DFO), parathyroid hormone (PTH), fragments of
23 PTH, antimicrobials, antibiotics, antibacterial agents, anti-
24 fungal agents, daptomycin, vitamins; analogs, fragments,
25 mimetics and polyethylene glycol (PEG)-modified derivatives of
26 these compounds; and any combination thereof.

1 14. The dosage unit form of **claim 11**, wherein the
2 biologically active agent comprises interferon, cromolyn
3 sodium sodium chromoglycate, disodium chromoglycate,
4 daptomycin, analogs, fragments, mimetics and polyethylene
5 glycol (PEG)-modified derivatives of these compounds or
6 combinations thereof.

1 15. The dosage unit form of **claim 11**, wherein the
2 biologically active agent comprises interferon.

1 16. The dosage unit form of **claim 11**, wherein the
2 biologically active agent comprises sodium cromolyn.

1 17. The dosage unit form of **claim 11**, wherein the
2 biologically active agent comprises daptomycin, an analog
3 thereof, or mixtures thereof.

1 18. The dosage unit form of **claim 10**, wherein the dosage
2 unit form is in the form of a tablet, a capsule, a particle, a

3 powder, a sachet, or a liquid.

1 19. The dosage unit form of claim 10, wherein the dosing
2 vehicle is liquid selected from the group consisting of water,
3 25% aqueous propylene glycol, phosphate buffer, 1,2-propane
4 diol, ethanol, and any combination thereof.

1 20. A method for administering a biologically-active
2 agent to an animal in need of the agent, the method comprising
3 administering orally to the animal the composition of claim 3.

1 21. A method for preparing a composition comprising
2 mixing:

- 3 (A) at least one active agent;
4 (B) the compound of claim 1; and
5 (C) optionally, a dosing vehicle.

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(54) Title: (5-(2-HYDROXY-4-CHLOROBENZOYL) AMINOVALERIC ACID AND SALTS THEREOF AND COMPOSITIONS CONTAINING THE SAME FOR DELIVERING ACTIVE AGENTS

(57) Abstract: (5-(2-hydroxy-4-chlorobenzoyl) aminovaleric acid, salts thereof, and compositions containing the same for the delivery of active agents are provided. Methods of administration, treatment of disease and preparation are provided as well.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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US CL : 562/444; 514/563; 252/182.31

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B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
~~NONE~~

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CASONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,773,647 A (LEON-BAY et al) 30 June 1998, column 27, compound 109, column 35, compound 141, column 41, compound 166, and claims.	1-21

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	"T" Later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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